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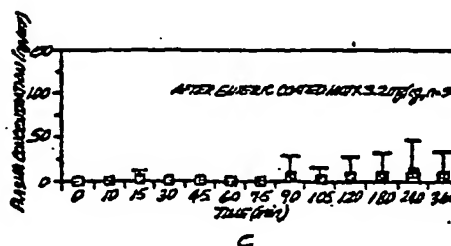
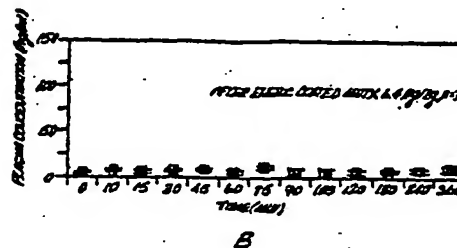
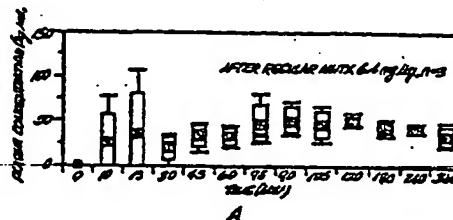
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(54) Title: USE OF METHYLNALTREXONE AND RELATED COMPOUNDS

(57) Abstract

A method for preventing or treating opioid induced side effects including dysphoria, pruritus, urinary retention and gastrointestinal dysfunction and non-opioid induced changes in gastrointestinal motility. The method comprises administering methylnaltrexone or another quaternary derivative of noroxymorphone to a patient prior to the administration of an opioid or after the onset of side effects induced by the administration of an opioid, wherein the methylnaltrexone or quaternary derivative is administered by the route selected from the group consisting of intravenous, intramuscular, transmucosal, transdermal, and oral administration, preferably administered orally in an enterically coated form.



## USE OF METHYLNALTREXONE AND RELATED COMPOUNDS

### CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of Serial No. 09/120,703 filed July 22, 1998, which is a continuation-in-part of Serial No. 08/962,742 filed November 3, 1997, the disclosures of both applications being incorporated herein by reference.

### FIELD OF THE INVENTION

The present invention is directed at the treatment of certain side effects associated with the use of opioids as analgesics. In particular the present invention is directed toward treating opioid-induced dysphoria, opioid-induced pruritus, opioid-induced urinary retention, opioid-and non-opioid-induced inhibition of gastric emptying and inhibition of gastrointestinal motility, and constipation.

### BACKGROUND OF THE INVENTION

Opioids are effective analgesics. However, their use is associated with a number of undesirable side effects. One of these side effects is pruritus, or itching. Pruritus is a common side effect associated with the use of opioids and may be very severe. Pruritus can occur when the opioid is administered intramuscularly, intravenously, transdermally, transmucosally or intrathecally.

It is believed that the opioid induced pruritus results from the release of histamine in response to the administration of opioids. Opioids are thought to stimulate histamine release by binding to opioid receptors on the central nervous system. This, in turn, causes peripheral nerves and histamine containing cells to release histamine.

Based on this theory a number of treatments have been used to alleviate opioid induced pruritus. The first is the use of antihistamines. However, antihistamines have a variable effect on opioid induced pruritus. Additionally, the use of antihistamines, when effective, only treats the symptom after it has occurred, rather than preventing its occurrence.

Another undesirable side effect of opioids is urinary retention, or the patient's inability to spontaneously empty his or her bladder. This urinary retention is a common side effect that can occur when opioids or related compounds are administered intramuscularly, intravenously, transmucosally, transdermally, or intrathecally. It is not clear why opioids cause urinary retention, but it is thought to be related to the central anticholinergic stimulation that opioids induce. Based on this theory, a number of cholinergic-type drugs have been used to treat urinary retention. However, due to the side effects of cholinergic drugs, catheterization of the bladder with a tube to drain urine remains the mainstay of treatment.

Another opioid-induced side effect is dysphoria, a feeling of unpleasantness or discomfort. Many subjects, especially those without pain, report unpleasant psychomimetic responses to the administration of an opioid alone. These responses have been previously attributed to activation of centrally located opioid receptors. This opioid-induced dysphoria is commonly treated by the addition of other drugs, such as benzodiazepines, to decrease the dysphoria or to blunt the recall of the dysphoria. These drugs, however are associated with increased levels of sedation and may enhance respiratory depression caused by the opioid.

Another side effect is constipation. Opioid-induced changes in gastrointestinal motility are almost universal when these drugs are used to treat pain, and at times may limit their use, leaving the patient in pain. Common treatments of bulking agents and laxatives have limited efficacy and may be associated with side effects such as electrolyte imbalances.

One treatment for side effects such as pruritis, urinary retention, dysphoria, and inhibited gastrointestinal motility is the use of opioid antagonists which cross the blood-brain-barrier, or which are administered directly into the central nervous system. Opioid antagonists such as naltrexone and naloxone have been administered intramuscularly or orally to treat opioid induced pruritus. Naltrexone and naloxone are highly lipid soluble and rapidly diffuse across biological membranes, including the blood-brain-barrier. However, naltrexone, naloxone and other opioid antagonists also reduce the analgesic effect of the opioid being used.

Many quaternary amine opioid antagonist derivatives, such as methylnaltrexone, do not reduce the analgesic effect of the opioids. These quaternary amine opioid antagonist derivatives, which have a relatively higher polarity and reduced lipid solubility when compared to the tertiary forms of the drugs, were specifically developed to not traverse the blood-brain-barrier or to traverse it at a greatly reduced rate. Since these quaternary opioid antagonist derivatives do not cross the blood-brain-barrier, peripheral administration of these antagonists would not be expected to be effective in the treatment of an opioid induced side effect caused by the opioid within the central nervous system. In fact, experiments show that to be effective in blocking the opioid receptors in the central nervous system, these antagonists must be injected directly into the central nervous system. However, injection of drugs directly into the central nervous system is undesirable since it increases the possibility of introducing bacterial or viral contamination to the central nervous system.

It is desirable in the treatment of many conditions to have oral medications with prolonged effects. Such oral medications are particularly desirable both for the treatment of opioid-induced side effects (such as urinary retention, pruritus, and some forms of constipation) and for the treatment of nonopioid-induced side effects (such as other forms of constipation and delayed gastric emptying or inhibition of gastrointestinal motility from any cause such as abdominal surgery or inflammation, or excessive vagal stimulation).

1  
5 It is further desirable to develop a method for the prevention of opioid induced dysphoria, opioid induced pruritus, urinary retention, opioid-or nonopioid-induced delayed gastric emptying from enteric feeding, inhibition of gut motility, and constipation, which does not counteract the analgesic effects of the opioid, or risk increased levels of pain. Ideally, such a treatment has few side effects either due to low drug toxicity or because administration of small amounts are effective and/or administration results in low circulating levels of the drug.

## 10 SUMMARY OF THE INVENTION

The present invention is directed at methods for preventing and treating opioid-induced pruritus, opioid-induced urinary retention, opioid-or nonopioid-induced inhibition of gastric emptying, opioid-or nonopioid-induced inhibition of gastrointestinal motility, and opioid-or nonopioid-induced constipation.

15 The method for preventing opioid-induced side effects, including dysphoria, pruritus, urinary retention, inhibition of gastric emptying, decreased gut motility, and constipation, comprises administering methylnaltrexone or enterically coated methylnaltrexone, or other quaternary derivatives of noroxymorphone as disclosed in U.S. Patent No. 4,176,186 to Goldberg *et al.* (herein incorporated by reference) to a patient prior to or simultaneously with the  
20 administration of an opioid wherein the route of administration is selected from the group consisting of intravenous, intramuscular, intraperitoneal, transmucosal, transdermal, and oral administration in a standard or enterically coated preparation.

The method for treating opioid-induced side effects, including dysphoria, pruritus, urinary retention, inhibition of gut motility and constipation, comprises administering methylnaltrexone or enterically coated methylnaltrexone, or other quaternary derivatives of noroxymorphone, to a patient after the onset of the side effect, wherein the route of administration is selected from the group consisting of intravenous, intramuscular, transmucosal, transdermal and oral  
25 administration in a standard or enterically coated preparation.

The method for preventing nonopioid-induced side effects, including gastrointestinal dysfunction (e.g., inhibition of gastric emptying, of gastrointestinal motility and constipation), comprises administering methylnaltrexone or enteric coated methylnaltrexone, or other quaternary derivatives of noroxymorphone, to a patient prior to the development of the side effects wherein the route of administration is selected from the group consisting of intravenous, intramuscular, transmucosal, transdermal and oral administration in a standard or enterically  
30 coated preparation.

The method for treating nonopioid-induced side effects, including inhibition of gastric emptying by enteric feeding and constipation, comprises administering methylnaltrexone or enteric coated methylnaltrexone, or other quaternary derivatives of noroxymorphone, to a patient  
35

1  
after the onset of the side effect, wherein the route of administration is selected from the group  
consisting of intravenous, intramuscular, transmucosal, transdermal and oral administration in  
5 a standard or enterically coated preparation.

#### DETAILED DESCRIPTION OF DRAWINGS :

FIG. 1A is a graph representing plasma concentrations of MNTX following administration  
of 6.4 mg/kg of uncoated MNTX.

10 FIG. 1B is a graph representing plasma concentrations of MNTX following administration  
of 6.4 mg/kg of enterically coated MNTX.

FIG. 1C is a graph representing plasma concentrations of MNTX following administration  
of 3.2 mg/kg of enterically coated MNTX.

15 FIG. 2 illustrates the reversal of morphine's effect on oral-cecal transit time following  
administration of 6.4 mg/kg of uncoated MNTX. The darker line represents the average of all  
points of a given treatment.

FIG. 3 illustrates the reversal of morphine's effect on oral-cecal transit time and its  
decrease below baseline following administration of 6.4 mg/kg of enterically coated MNTX.  
The darker line represents the average of all points of a given treatment.

20 FIG. 4 illustrates the reversal of morphine's effect on oral-cecal transit time following  
administration of 3.2 mg/kg of enterically coated MNTX. The darker line represents the average  
of all points of a given treatment.

#### 25 DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to methods for preventing and treating opioid-induced  
dysphoria, opioid-induced pruritus, opioid-induced urinary retention, opioid-or  
nonopioid-induced inhibition of gastric emptying or inhibition of gastrointestinal mobility, and  
opioid-or nonopioid-induced constipation. When used as a treatment for these opioid-and  
30 nonopioid-induced side effects, orally administered, particularly if enterically coated,  
methylnaltrexone (MNTX) or other quaternary derivatives of noroxymorphone (QDNM)  
provides prolonged relief of the side effects. MNTX has been demonstrated to have the ability  
to block the gastrointestinal effects of opioids on motility when administered intravenously or  
orally.

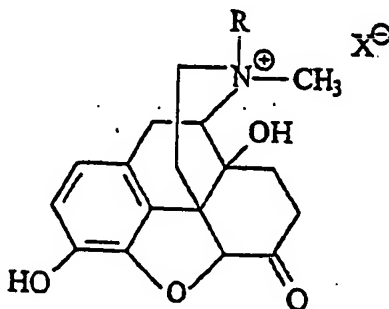
35 The oral administration of non-enterically coated MNTX is associated with plasma levels  
with an early peak (20 min) and prolonged presence (half-life of about 3 hours after single dose  
of 6.4 mg/kg). However, an enteric coating on the QDNM, designed to prevent dissolution and  
subsequent absorption of the drug in the stomach, would be expected to produce delayed

elevation of plasma levels of the QDNM, and to produce a lower peak plasma level. Surprisingly, however, administration of enterically coated MNTX has been found to result in substantially lower plasma levels as compared to non-enterically coated MNTX at the same dosage level, and surprisingly and unexpectedly resulted in enhanced efficacy in the reversal of opioid-induced decreases in gastrointestinal motility. In fact, it has been found that as compared to non-enterically coated MNTX, a significantly lower dose, e.g., less than half the amount of coated MNTX can be used if enterically coated to achieve the same levels of relief of opioid-induced constipation. Moreover, such reduced dosage levels of MNTX administered with an enteric coating results in exceedingly low peak and sustained plasma levels of MNTX, greatly reducing the potential adverse side effects of the MNTX. This novel improvement in the clinical indication for use of MNTX has led to an increased therapeutic index for this drug.

When used as a treatment for the opioid- and nonopioid-induced side effects of constipation and reduction of gastrointestinal motility, orally administered, particularly if enterically coated, MNTX or other quaternary derivatives of noroxymorphone provide prolonged relief of the side effects. MNTX has been demonstrated to have the ability to block the gastrointestinal effects of opioids on motility when administered intravenously or orally.

Furthermore, for treatment or prevention of constipation and delayed gastrointestinal emptying, whether caused by extrinsic or endogenous opioids, enteric coating surprisingly allows for equal or better efficacy despite lower plasma levels. Idiopathic constipation, i.e., that due to causes other than exogenous administration of opioids, may be mediated by opioid sensitive mechanisms. Endogenous opioid receptors have been identified in the gut, and these receptors may modulate gut motility. Thus, administration of an opioid antagonist with peripheral action, such a methylnaltrexone or other quaternary derivatives of noroxymorphone, would block the effects of endogenous opioids.

Quaternary derivatives of noroxymorphone are described in full in Goldberg *et al.*, (*supra*), and in general are represented by the formula:





1 wherein R is allyl or a related radical such as chlorallyl, cyclopropyl-methyl or propargyl, and X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion.

5 The presently preferred quaternary derivative of noroxymorphone is methylnaltrexone. Methylnaltrexone is a quaternary amine derivative of naltrexone. Methylnaltrexone has been found to have only 2 to 4% of the opiate antagonistic activity of naltrexone *in vivo* due to its inability to pass the blood-brain-barrier and bind to the opiate receptors in the central nervous system.

10 Opioids are typically administered at a morphine equivalent dosage of: 0.005 to 0.15 mg/kg body weight for intrathecal administration; 0.05 to 1.0 mg/kg body weight for intravenous administration; 0.05 to 1.0 mg/kg body weight for intramuscular administration; 0.05 to 1.0 mg/kg body weight/hour for transmucosal or transdermal administration. By "morphine equivalent dosage" is meant representative doses of other opioids which equal one milligram of morphine, for example 10 mg meperidine, 1 mg methadone, and 80 µg fentanyl.

15 In accordance with the present invention, methylnaltrexone is administered at a dosage of: 0.03 to 1.0 mg/kg body weight for intravenous administration; 0.03 to 1.0 mg/kg body weight for intramuscular administration; 0.03 to 1.0 mg/kg body weight for transmucosal administration and 0.1 to 80.0 mg/kg body weight for oral administration, including enterically coated methylnaltrexone.

20 The administration of the methylnaltrexone is preferably commenced prior to administration of the opioid to prevent opioid-induced dysphoria, pruritus, urinary retention, inhibition of gastric emptying or gastrointestinal motility, or constipation. It is desirable to commence administration of methylnaltrexone about 5 minutes (for parenteral MNTX administration) or 20 minutes (for enteral MNTX administration) prior to administration of opioids in order to prevent opioid-induced side effects. It is also preferable to administer the methylnaltrexone prior to the onset of nonopioid-induced gastric dysfunction symptoms, inhibition of gastric emptying, of gastrointestinal motility, or constipation, in order to prevent these symptoms from manifesting. While the prevention of symptoms is preferred, methylnaltrexone administration may also be commenced concurrent with or after the administration of the opioid or after the onset of opioid induced symptoms as a treatment for those symptoms.

25 30 35 Methylnaltrexone is rapidly absorbed after oral administration from the stomach and bowel. Initial plasma levels of the drug are seen within 5-10 minutes of the administration of non-enteric coated compound. Addition of an enteric coating which prevents gastric absorption is associated with lower plasma levels of the methylnaltrexone. Surprisingly, the addition of an enteric coating (i.e., a coating which will prevent degradation or release in the stomach, but will

1 release drug in the small and large bowel) enhances the efficacy of methylnaltrexone in the  
prevention of decreases in gut motility by intravenously administered opioids (morphine).

5 For intravenous administration, methylnaltrexone is formulated with saline or other  
physiologically acceptable carriers; for intramuscular administration, the methylnaltrexone is  
formulated with saline or other pharmacologically acceptable carriers; for transmucosal  
administration the methylnaltrexone is formulated with a sugar and cellulose mix or other  
10 pharmacologically acceptable carriers known in the art; and for oral administration, the  
methylnaltrexone is formulated with pharmacologically acceptable binders to make a tablet or  
capsule with or without an enteric coating. Methods for such formulations are well known to  
those skilled in the art.

15 In a preferred embodiment for the prevention and/or treatment of constipation and  
inhibition of gastrointestinal motility, the QDNM or MNTX is enterically coated and  
administered orally. For oral administration, the QDNM or methylnaltrexone is formulated with  
pharmacologically acceptable binders to make a tablet or capsule with an enteric coating. An  
enteric coating is one which remains intact during passage through the stomach, but dissolves  
and releases the contents of the tablet or capsule once it reaches the small intestine. Most  
20 currently used enteric coatings are those which will not dissolve in low pH environments, but  
readily ionize when the pH rises to about 4 or 5, for example synthetic polymers such as  
polyacids having a  $pK_a$  of 3 to 5.

25 The enteric coating may be made of any suitable composition. Suitable enteric coatings  
are described, for example, in U.S. Patent Nos. 4,311,833 to Namikoshi, et al.; 4,377,568 to  
Chopra; 4,385,078 to Onda, et al.; 4,457,907 to Porter; 4,462,839 to McGinley, et al.; 4,518,433  
to McGinley, et al.; 4,556,552 to Porter, et al.; 4,606,909 to Bechgaard et al.; 4,615,885 to  
Nakagame, et al.; 4,670,287 to Tsuji; 5,536,507 to Abramowitz, et al.; 5,567,423 to Ying, et al.;  
5,591,433 to Michael, et al.; 5,597,564 to Ying, et al.; 5,609,871 to Michael, et al.; 5,614,222 to  
Kaplan; 5,626,875 to Rodes, et al.; and 5,629,001 to Michael, et al., all of which are incorporated  
herein by reference.

30 Preferred enteric coating compositions include alkyl and hydroxyalkyl celluloses and their  
aliphatic esters, e.g., methylcellulose, ethylcellulose, hydroxyethylcellulose,  
hydroxypropylcellulose, hydroxybutylcellulose, hydroxyethylethylcellulose,  
hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, hydroxypropylcellulose phthalate,  
hydroxypropylmethylcellulose phthalate and hydroxypropylmethylcellulose acetate succinate;  
35 carboxyalkylcelluloses and their salts, e.g., carboxymethylethylcellulose; cellulose acetate  
phthalate; cellulose acetate trimellitate, polycarboxymethylene and its salts and derivatives;  
polyvinyl alcohol and its esters: polyvinyl acetate phthalate; polycarboxymethylene copolymer  
with sodium formaldehyde carboxylate; acrylic polymers and copolymers, e.g., methacrylic

1 acid-methyl methacrylic acid copolymer and methacrylic acid-methyl acrylate copolymer; edible  
oils such as peanut oil, palm oil, olive oil and hydrogenated vegetable oils; polyvinylpyrrolidone;  
5 polyethylene glycol and its esters: natural products such as shellac, and zein.

Other preferred enteric coatings include polyvinylacetate esters, e.g., polyvinyl acetate  
phthalate; alkylene glycolether esters of copolymers such as partial ethylene glycol  
monomethylether ester of ethylacrylate-maleic anhydride copolymer or diethyleneglycol  
monomethylether ester of methylacrylate-maleic anhydride copolymer, N-butylacrylate-maleic  
10 anhydride copolymer, isobutylacrylate-maleic anhydride copolymer or ethylacrylate-maleic  
anhydride copolymer; and polypeptides resistant to degradation in the gastric environment, e.g.,  
polyarginine and polylysine. Other suitable coatings and methods to make and use such  
formulations are well known to those skilled in the art (see, e.g., Remington: The Science and  
Practice of Pharmacy, 19th ed. (1995) Mack Publishing Company, Easton, Pennsylvania; herein  
15 incorporated by reference).

Mixtures of two or more of the above compounds may be used as desired. The presently  
preferred enteric coating comprises cellulose acetate phthalate.

The enteric coating material may be mixed with various excipients including plasticizers  
such as triethyl citrate, acetyl triethyl citrate, diethyl phthalate, dibutyl phthalate, dibutyl  
20 subacetate, dibutyl tartrate, dibutyl maleate, dibutyl succinate and diethyl succinate and inert fillers  
such as chalk or pigments.

The composition and thickness of the enteric coating may be selected to dissolve  
immediately upon contact with the digestive juice of the intestine. Alternatively, the  
composition and thickness of the exterior coating may be selected to be a time-release coating  
25 which dissolves over a selected period of time, as is well known in the art.

The amount of enteric coating depends on the particular enteric coating composition used  
and is preferably sufficient to substantially prevent the absorption of QDMN or MNTX in the  
stomach.

Hydroxyalkyl celluloses and their aliphatic esters, carboxyalkyl celluloses and their salts,  
30 polycarboxymethylene and its salts and derivatives, polyvinyl alcohol and its esters,  
polycarboxymethylene copolymer with sodium formaldehyde carboxylates,  
poly-vinylpyrrolidone, and polyethylene glycol and its esters can be applied as enteric coatings  
by first dissolving the compound in a minimum amount of water. Alcohol is then added to the  
point of incipient cloudiness. The mixture can then be applied by conventional techniques.

35 Application of cellulose acetate phthalate may be accomplished by simply dissolving the  
cellulose acetate phthalate in a minimum amount of alcohol and then applying by conventional  
techniques. Hydrogenated vegetable oils may be applied by first dissolving the oil in a minimal  
amount of a non-polymer solvent, such as methylene chloride, chloroform or carbon

tetrachloride, then adding alcohol to the point of incipient cloudiness and then applying by conventional techniques.

In a particularly preferred embodiment, the MNTX is coated with Eudragit L100 or S100, a methacrylic acid copolymer enteric coating, at a 50% coating level to provide stability at gastric pH and dissolution at gut pH per a US Pharmacopeia (USP) standard for enteric coatings.

Any art-known transdermal application may be used, but transdermal administration is preferably via a patch applied to the skin with a membrane of sufficient permeability to allow diffusion of MNTX at a fixed rate in the range of 1.0 to 10.0 mg/hr. The rate of administration may be varied by varying the size of the membrane contact area and/or applying an electrical wiring potential to a drug reservoir. The patch preferably holds 25 mg to 1 gram of available drug in the reservoir plus additional drug as needed for the mechanics of the system.

In the above description, methylnaltrexone is used as an example of a particularly effective QDNM. It is apparent that other QDNM's may be used as desired.

The following Examples are intended to illustrate aspects of the invention and are not to be construed as limitations upon it. The methylnaltrexone used in the following Examples was manufactured by Mallinckrodt Pharmaceuticals, St. Louis, MO. The Enteric Coating was manufactured by Coating Place, Inc., Verona, WI.

#### EXAMPLE 1

Ten patients were treated with morphine sulfate administered directly to the central nervous system or intravenously. The morphine sulfate was administered at 0.1 mg/kg body weight. The patients in the study had been treated for pain resulting from surgery. All the patients exhibited pruritus as a side effect of the morphine sulfate administration. Subsequent to the onset of the pruritus, methylnaltrexone, at a dosage of 0.3 mg/kg of body weight was administered intravenously as a saline solution containing methylnaltrexone in a concentration of 5 mg/ml to each of the patients. Eighty percent of the 10 patients exhibited relief from the pruritus sixty minutes after receiving methylnaltrexone.

In a control group, 8 patients were treated with morphine sulfate administered directly to the central nervous system or intravenously. The morphine sulfate was administered at 0.1 mg/kg body weight. The patients in the study had been treated for pain resulting from surgery. All the patients exhibited pruritus as a side effect of the morphine sulfate administration. A placebo, saline at a volume equivalent to the volume administered to patients receiving active drug, was administered intravenously to each of the patients. Only 50% of the patients exhibited relief from the pruritus within sixty minutes.

The study indicates that methylnaltrexone was effective in treating pruritus induced by morphine sulfate.

**EXAMPLE 2****EFFICACY OF ENTERIC COATING OF METHYLNALTREXONE**

Morphine (0.05 mg/kg intravenous) was administered to three volunteers after the oral administration of placebo, methylnaltrexone (6.4 mg/kg) in a gelatin capsule (which dissolves readily in the stomach), or methylnaltrexone after enteric coating (12.8 mg/kg of substance to yield a mass of 6.4 mg/kg methylnaltrexone incorporated) which has decreased release and absorption in the stomach. Oral-cecal transit time was measured using the lactulose-hydrogen breath test. Plasma levels of methylnaltrexone were measured and after the enteric coated preparation were lower. In each subject morphine alone increased the oral-cecal transit time by 20 -70 minutes, methylnaltrexone blocked this effect, and enteric coated methylnaltrexone blocked the effect to a similar or greater extent than the uncoated methylnaltrexone.

**EXAMPLE 3****ENHANCEMENT OF ENTERIC FEEDING**

Two patients receiving morphine (375 mg/day and 18 mg/day) and receiving enteric tube feedings of 200 ml every four (4) hours were studied. The first patient had residual stomach contents of 50cc to 100cc, or 22.0-58.8% of administered feedings measured every 4 hours during a 24 hour control period. Prior to drug administration the residual volume had increased to 260 cc or > 100% of previous feeding volume. Methylnaltrexone, 0.45 mg/kg, was administered intravenously every 4 hours for 24 hours, after the control period. After the first dose (4 hours) of MNTX, the residual was 150cc or 58% of the previous bolus feed, after the 3rd dose (12 hours) the residual was 75cc or 30% of the previous feed, after the 5th dose (20 hours) the residual was 22cc or 13% of the previous feed and after the 6th and final dose (24 hours) the residual was 8cc or 5.5% of previous feed. The follow-up residual sampling after the final drug-tube feed interval had increased to 50cc or 38% of previous feed.

The second patient had greater than 200cc residual or 100% of previous feedings on two consecutive samplings, that is 8 hrs and 4 hrs before drug administration. After initiation of Methylnaltrexone, 0.45 mg/kg, administered intravenously every 4 hours, the first residual (4 hrs) was 0cc, the second residual (8 hrs) was 24cc or 15% of previous bolus feed.

**EXAMPLE 4****TREATMENT OF URINARY RETENTION**

Subjects receiving morphine at a variety of doses (via patient controlled analgesia -PCA) who experience urinary retention are administered Methylnaltrexone 0.45 mg/kg intravenously or a placebo. Those treated with Methylnaltrexone have resolution of their symptoms, while those administered placebo go on to require additional therapy (usually urinary catheterization).

**EXAMPLE 5**

In a double-blind randomized placebo-controlled study, we evaluated the efficacy of oral methylnaltrexone to decrease subjective effects after administering morphine to 10 normal human volunteers. After intravenous morphine injection (0.05 mg/kg), significant increases in subjective ratings were obtained on "nauseous", "skin itch", "stimulated", and "flushing". Compared to baseline, significant increases were obtained on "nauseous", "Skin itch", "stimulated", and "flushing" ratings after placebo and morphine administration ( $P < 0.05$ ,  $P < 0.05$ ,  $P < 0.01$  and  $P < 0.01$ , respectively). Oral methylnaltrexone (19.2 mg/kg) significantly decreased these four ratings ( $P < 0.05$ ,  $P < 0.05$ ,  $P < 0.01$  and  $P < 0.01$ , respectively) compared to placebo and morphine and resulted in no change when compared to baseline. Plasma methylnaltrexone concentrations were also measured and correlation between pharmacological effects of the compound and its plasma levels was shown. Our results indicate that methylnaltrexone decreases dysphoria and some other undesirable subjective effects associated with opioid medications.

**EXAMPLE 6****EFFECTS OF ENTERICALLY COATED MNTX ON ORAL-CECAL TRANSIT  
TIME AND PLASMA LEVELS OF MNTX**

Oral methylnaltrexone, whether enterically coated or uncoated, was shown to reverse the inhibitory effects of opioid administration on gastrointestinal motility as measured by oral-cecal transit time. As compared to non-enterically coated MNTX, however, treatment with enterically coated MNTX enhanced the efficacy of the drug at a lower dose while producing lower plasma levels of MNTX.

Subjects were divided into five treatment groups A-E. With the exception of subjects in Group A, who were given a placebo in place of morphine, all were given an intravenous dose of morphine at 0.05 mg/kg. Prior to morphine administration, subjects were given either a placebo or MNTX in various doses and formulations (see Table 1). The subjects in Group A and B were given a placebo in place of MNTX. Group C received uncoated MNTX at 6.4 mg/kg, Group D received enterically coated MNTX at 6.4 mg/kg active drug, and Group E received enterically coated MNTX at 3.2 mg/kg active drug. Table 1 shows the treatments for each group.

TABLE 1

Group	Treatment combination	FIG.
A	placebo	
B	morphine (0.05 mg/kg)	
C	placebo	Fig. 2
D	methylbaltrexone uncoated (6.4 mg/kg)	Fig. 3
	methylbaltrexone enteric coated (6.4 mg/kg)	
E	active drug	
	methylbaltrexone enteric coated (3.2 mg/kg)	Fig. 4
	active drug	

Plasma levels of MNTX were measured following administration of morphine and MNTX or placebo several times over the duration of the six hour monitoring period, at the times shown in FIG. 1. Measurements of plasma and urine MNTX levels were determined by high performance liquid chromatography (HPLC) using the modified method originally reported by Kim *et al.* (1989) *Chromatographia* 28:359-63, herein incorporated by reference). Methylbaltrexone was separated from plasma by solid phase extraction (SPE). Plasma samples (100-500  $\mu$ l) diluted in water with the internal standard (naltrexone) were passed through SPE columns. Prior to use, the columns were conditioned by methanol and washed with water. The analytes were eluted from the columns by the mixture of n-propanol and trifluoroacetic acid (25 mM) aqueous solution prepared in 2:1 proportion. The eluate was evaporated to dryness in a stream of nitrogen at 55°C. The residue was reconstituted in the mobile phase, filtered through a nylon HPLC syringe filter and subjected to HPLC analysis. A Shimadzu Corporation (Kyoto, Japan) HPLC system was used. It consisted of the LC-10AD pump, SCL-10A system controller, and SIL-10A auto injector equipped with sample cooler. Used HPLC Analytical Column made by Phenomenex (Prodigy C8, Torrance, CA). The electrochemical detector (ESA Coulochem, model 5100A) worked at the following settings: detector 1, +360 mV, detector 2 +600 mV, guard cell +650 mV. Data were collected with the use of EZChrom 2-2 HPLC software. The mobile phase consisted of 50 mM sodium acetate, 7.5% methanol at pH 4.2. The system was calibrated daily in the range of 5 - 100 ng/ml (3 point calibration). Practical limit of detection for plasma samples was approximately 2 ng/ml (100 pg/injection).

Figure 1 shows the plasma levels of MNTX following the treatments in Groups C, D, and E. In Fig. 1A, MNTX plasma levels in Group C (given 6.4 mg/kg MNTX, uncoated) peaked at about 15 min. post-MNTX administration and remained at a roughly constant level (between about 35-50 ng/ml) for the duration of the study period (6 hours). Group D, given 6.4 mg/kg MNTX in an enterically coated formulation, exhibited a constant low plasma level of MNTX (under 10 ng/ml) for the duration of observation (see FIG. 1B). Group E, given 3.2 mg/kg

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MNTX in an enterically coated formulation, showed plasma levels of MNTX over the course of observation that were undetectable or at the lower limit of detection of the assay (see FIG. 1C).

5

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Oral-cecal transit time was used as a measure of gut motility and propensity for constipation. Oral-cecal transit time was measured by the lactulose-breath hydrogen method. Group A demonstrated normal transit times as previously described in the literature (Yuan *et al.* (1996) *Clin. Pharmacol. Ther.* 59:469-475; Yuan *et al.* (1997) *Clin. Pharmacol. Ther.* 61:467-475, both herein incorporated by reference). Group B had prolongation of their oral-cecal transit times by 50-100%, while Groups C (FIG. 2) and E (FIG. 4) had their transit times return to baseline levels. Group D showed an obvious decrease in oral-cecal transit time (FIG. 3).

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As demonstrated in FIGS. 1-4, enterically coated MNTX provides the therapeutic effects on gastrointestinal motility of uncoated MNTX, but requires a lower dose of active drug and results in significantly reduced plasma levels of MNTX. Patients provided with a dose of 6.4 mg/kg of uncoated MNTX had gut motility return to baseline following morphine administration (FIG. 2) and showed plasma MNTX levels of over 40 ng MNTX/ml, while patients given the same dose in an enterically coated formulation showed oral-cecal transit times below baseline levels (FIG. 3) and plasma MNTX levels under 10 ng/ml. Enterically coated formulations of MNTX with one half the dose of active drug (3.2 mg/kg) were required to return oral-cecal transit times to normal without increasing gut motility. At this dosage, plasma levels of MNTX were negligible.

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As with most drugs, it is desirable to maintain the lowest possible systemic levels of MNTX which are sufficient to provide the desired therapeutic effect. For example, elevated circulating levels of MNTX can result in orthostatic hypotension. The present discovery provides an unexpected means to avoid such undesirable drug side effects by lowering the dose administered and subsequently minimizing circulating levels of the drug. Since endogenous and externally supplied opioid-induced inhibition of gastrointestinal motility and constipation is thought to result from opioid receptors located within the gastrointestinal tract, enterically coated MNTX or other QDNMs may provide a local administration of the drug that does not require a circulating level for effective prevention or treatment of symptoms. Thus, the amount and/or frequency of drug administered can be reduced.

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The preceding description and Examples are intended to be illustrative. Those skilled in the art to which the invention pertains will appreciate that alterations and changes in the described protocols may be practiced without departing from the meaning, spirit, and scope of this invention. Therefore, the foregoing description should be read consistent with and as support to the following claims, which are to have their fullest and fair scope.



Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements,

5 integers or steps.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base  
10 or were common general knowledge in the field relevant to the present invention as it existed in Australia before the priority date of each claim of this application.

15



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method for preventing opioid induced side effects comprising administering a quaternary derivative of noroxymorphone to a patient prior to the administration of an opioid, the side effect selected from the group consisting of dysphoria, pruritus, and urinary retention.
2. A method for treating opioid induced side effects comprising administering quaternary derivatives of noroxymorphone to a patient subsequent to the administration of an opioid, the side effect selected from the group consisting of dysphoria, pruritus, and urinary retention.
3. The method as recited in claim 1 or 2 wherein the quaternary derivative is methylnaltrexone.
4. The method as recited in claim 1, 2 or 3 wherein the side effect is dysphoria.
5. The method as recited in claim 1, 2 or 3 wherein the side effect is pruritus.
6. The method as recited in claim 1, 2 or 3 wherein the side effect is urinary retention.
7. The method as recited in claim 3 wherein the methylnaltrexone is administered by the route selected from the group consisting of intravenous, intramuscular, transmucosal, transdermal, and oral administration.
8. The method as recited in claim 1, 2 or 3 wherein the quaternary derivative is coated with an enteric coating.
9. The method as recited in claim 3 wherein the methylnaltrexone is administered at a dosage 0.03 to 1.0 mg/kg body weight for intravenous or intramuscular administration; 1.0 to 10.0 mg/kg for transdermal administration; and 0.1 to 80 mg/kg body weight for oral administration of methylnaltrexone.
10. The method as recited in claim 3 wherein the methylnaltrexone is administered orally as an enterically coated tablet at a dosage of about 0.1 to about 40 mg/kg body weight.
11. A method for preventing nonopioid induced gastrointestinal dysfunction comprising administering a quaternary derivative of noroxymorphone to a patient prior to the onset of the gastrointestinal dysfunction.
12. A method for treating nonopioid induced gastrointestinal dysfunction comprising administering a quaternary derivative of noroxymorphone to a patient after the onset of the gastrointestinal dysfunction.



13. The method of claim 11 or 12 wherein the quaternary derivative is methylnaltrexone.
14. The method as recited in claim 11 or 12 wherein the gastrointestinal dysfunction is selected from the group consisting of inhibition of gastric emptying and constipation.
15. The method as recited in claim 13 wherein the methylnaltrexone is administered by the route selected from the group consisting of intravenous, intramuscular, transmucosal, transdermal, and oral administration.
16. The method as recited in claim 13 wherein the methylnaltrexone is administered orally at a dosage of 0.1 to 80 mg/kg body weight.
17. The method as recited in claim 11, 12, or 13 wherein the quaternary derivative is formulated as a tablet and the tablet is coated with an enteric coating.
18. A method for preventing opioid induced inhibition of gastrointestinal motility comprising orally administering an enterically coated quaternary derivative of noroxymorphone to a patient prior to administration of an opioid, wherein substantially no quaternary derivative is released in the stomach.
19. The method of claim 18 wherein the quaternary derivative is methylnaltrexone.
20. The method of claim 18 or 19 wherein the inhibition of gastrointestinal motility is manifested as constipation.
21. The method of claim 19 wherein the methylnaltrexone is administered at a dosage of about 0.1 to about 10 mg/kg body weight.
22. The method of claim 19 wherein the methylnaltrexone is administered as an enterically coated tablet or capsule, or as enterically coated granules.
23. The method of claim 19 wherein the patient's plasma level of methylnaltrexone remains below 50 ng/mL.
24. A method for treating opioid induced inhibition of gastrointestinal motility comprising orally administering an enterically coated quaternary derivative of noroxymorphone to a patient subsequent to administration of an opioid, wherein substantially no quaternary derivative is released in the stomach.
25. The method of claim 24 wherein the quaternary derivative is methylnaltrexone.



26. The method of claim 24 or 25 wherein the inhibition of gastrointestinal motility is manifested as constipation.

27. The method of claim 25 wherein the patient's plasma level of methylnaltrexone remains below 50 ng/ml.

28. The method of claim 25 wherein the methylnaltrexone is administered at a dosage 0.1 to 40.0 mg of active drug per kg body weight.

29. The method of claim 25 wherein the methylnaltrexone is administered orally at a dosage of about 0.1 to about 10 mg/kg body weight.

30. The method of claim 19 wherein the methylnaltrexone is administered as an enterically coated tablet or capsule, or as enterically coated granules.

31. A method for treating opioid induced inhibition of gastrointestinal motility comprising orally administering an enterically coated quaternary derivative of noroxymorphone to a patient wherein the inhibition of gastrointestinal motility is induced by endogenous opioids.

32. The method of claim 19 wherein the enteric coating provides time release of the methylnaltrexone.

33. A composition when used for preventing or treating opioid-induced inhibition of gastrointestinal motility comprising an enterically coated quaternary derivative of noroxymorphone, which when orally administered to a patient releases substantially no quaternary derivative in the stomach, and when administered, induces peak and sustained plasma levels of the quaternary derivative that are substantially lower than such levels would be with the same dose of quaternary derivative that is non-enterically coated.

34. A composition as claimed in claim 33 in the form of a pill, tablet, capsule, or granules.

35. A composition as claimed in claim 33 where the quaternary derivative of noroxymorphone is methylnaltrexone.

36. The method of claim 18 or 24 wherein the patient's peak and sustained plasma levels of the quaternary derivative are below about 50 ng/ml.

37. The method of claim 18 or 24, wherein the patient's peak blood plasma levels are lower than they would be if 10% or more of the same dose of quaternary derivative were released in the stomach and the rest was released enterically.

38. A method of treating or preventing opioid induced inhibition of gastrointestinal motility comprising orally administering an enterically coated quaternary derivative of



noroxymorphone to a patient wherein the patient's peak plasma levels of the quaternary derivative do not exceed about 50 ng/ml.

39. The method of claim 38 wherein the patient's peak plasma levels  
5 of the quaternary derivative do not exceed about 40 ng/ml.

40. The method of claim 38 wherein the patient's peak plasma levels of the quaternary derivative do not exceed about 30 ng/ml.

10 41. The method of claim 38 wherein the patient's peak plasma levels of the quaternary derivative do not exceed about 20 ng/ml.

42. The method of claim 38 wherein the patient's peak plasma levels of the quaternary derivative do not exceed about 10 ng/ml.  
15

43. The method of claim 38 wherein the patient's peak plasma levels of the quaternary derivative do not exceed about 2 ng/ml.

44. A method for preventing surgery-induced inhibition of  
20 gastrointestinal motility comprising of administering a quaternary derivative of noroxymorphone.

45. A method for treating surgery-induced inhibition of  
gastrointestinal motility comprising administering a quaternary derivative of  
25 noroxymorphone.

46. The method as recited in claims 44 or 45 wherein the quaternary derivative of noroxymorphone is methylnaltrexone.

30 47. The method as recited in claims 44, 45 or 46 wherein the quaternary derivative is administered by the route selected from the group consisting of intravenous, intramuscular, transmucosal, transdermal, and oral administration.

35 48. The method as recited in claims 44, 45 or 46 wherein the quaternary derivative is coated with an enteric coating.



49. The method as recited in claim 46 wherein the methylnaltrexone is administered at a dosage 0.03 to 1.0 mg/kg body weight for intravenous or intramuscular administration; 1.0 to 10.0 mg/kg for transdermal administration; and 0.1 to 80 mg/kg body weight for oral administration of  
5 methylnaltrexone.

50. The method as recited in claim 46 wherein the methylnaltrexone is administered orally as an enterically coated tablet at a dosage of about 0.1 to about 40 mg/kg body weight.  
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51. The method according to claim 1 substantially as described with reference to any one of examples 1, 4 and 5.

52. The method according to claim 18 substantially as described with  
15 reference to example 3 or example 6.

53. A method for preventing idiopathic constipation comprising administering a quaternary derivative of noroxymorphone to a patient in an amount effective to prevent the constipation.  
20

54. A method for treating idiopathic constipation comprising administering a quaternary derivative of noroxymorphone to a patient in an amount effective to treat the constipation.

55. The method of claims 53 or 54, wherein the quaternary derivative of noroxymorphone is methylnaltrexone.

56. A method for treating inhibition of gastrointestinal motility comprising administering a quaternary derivative of noroxymorphone to a patient in an  
30 amount effective to treat the inhibition, wherein the inhibition of gastrointestinal motility is induced by an endogenous opioid.

57. The method of claim 56, wherein the quaternary derivative of noroxymorphone is methylnaltrexone.  
35



58. A method for preventing inhibition of gastrointestinal motility in a patient receiving an opioid for pain resulting from surgery comprising administering a quaternary derivative of noroxymorphone to the patient in an amount effective to prevent the inhibition.

5

59. A method for treating inhibition of gastrointestinal motility in a patient receiving an opioid for pain resulting from surgery comprising administering a quaternary derivative of noroxymorphone to the patient in an amount effective to treat the inhibition.

10

60. The method of claim 58 or claim 59, wherein the quaternary derivative of noroxymorphone is methylnaltrexone.

61. The method of claim 58 or claim 59 wherein the quaternary derivative  
15 of noroxymorphone is administered subsequent to the opioid.

62. The use of a quaternary derivative of noroxymorphone in the manufacture of a medicament for the prevention or treatment of opioid induced inhibition of gastrointestinal motility, wherein the quaternary  
20 derivative is enterically coated, and wherein when the quaternary derivative is orally administered to a patient, substantially no quaternary derivative is released in the stomach.

63. The use of a quaternary derivative according to claim 62, wherein the  
25 peak and sustained plasma levels of the quaternary derivative are substantially lower than such levels would be with the same dose of quaternary derivative that is non-enterically coated.

64. The use of a quaternary derivative of noroxymorphone according to  
30 claim 62, wherein the enterically coated quaternary derivative is in the form of a pill, tablet, capsule, or granule.

65. The use of a quaternary derivative of noroxymorphone according to claim 62, wherein the quaternary derivative is methylnaltrexone.

35



66. A method for treating or preventing inhibition of gastrointestinal motility comprising administering a quaternary derivative of noroxymorphone to a patient in an amount effective to treat the inhibition, wherein the inhibition of gastrointestinal motility is caused by abdominal surgery.

67. A method for treating or preventing inhibition of gastrointestinal motility comprising administering a quaternary derivative of noroxymorphone to a patient in an amount effective to treat the inhibition, wherein the inhibition of gastrointestinal motility is caused by inflammation.

68. A method for treating or preventing inhibition of gastrointestinal motility comprising administering a quaternary derivative of noroxymorphone to a patient in an amount effective to treat the inhibition, wherein the inhibition of gastrointestinal motility is caused by excessive vagal stimulation.

69. The method of any one of claims 66 to 68 wherein the quaternary derivative of noroxymorphone is methylnaltrexone.

70. Use of a quaternary derivative of noroxymorphone for the manufacture of a medicament for treating or preventing inhibition of gastrointestinal motility, wherein the inhibition of gastrointestinal motility is caused by abdominal surgery.

71. Use of a quaternary derivative of noroxymorphone for the manufacture of a medicament for treating or preventing inhibition of gastrointestinal motility, wherein the inhibition of gastrointestinal motility is caused by inflammation.

72. Use of a quaternary derivative of noroxymorphone for the manufacture of a medicament for treating or preventing inhibition of gastrointestinal motility, wherein the inhibition of gastrointestinal motility is caused by excessive vagal stimulation.





73. Use according to any one of claims 70 to 72 wherein the quaternary derivative of noroxymorphone is methylnaltrexone

Dated this thirtieth day of December 2002

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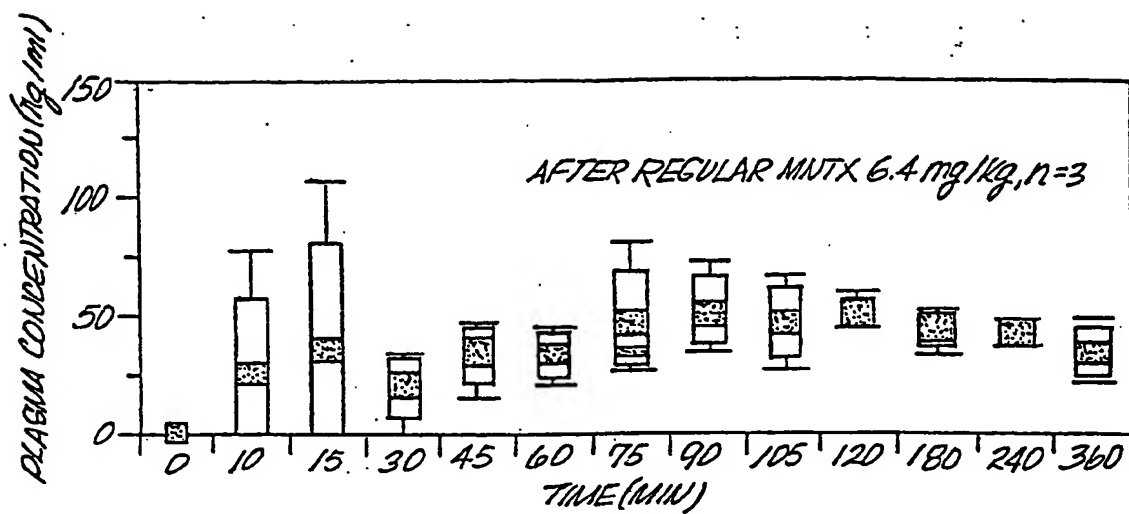


Fig. 1A

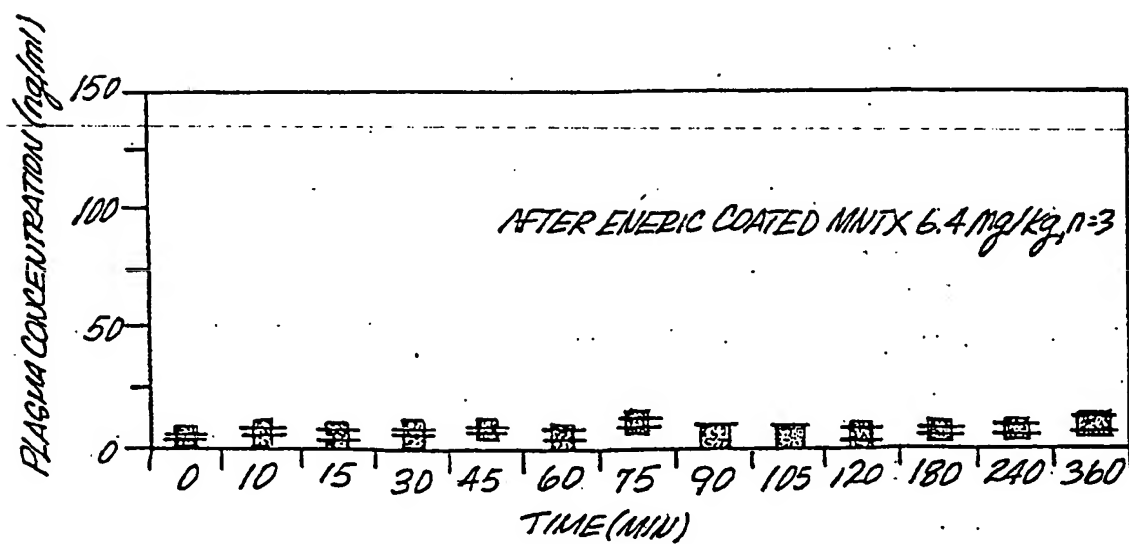


Fig. 1B

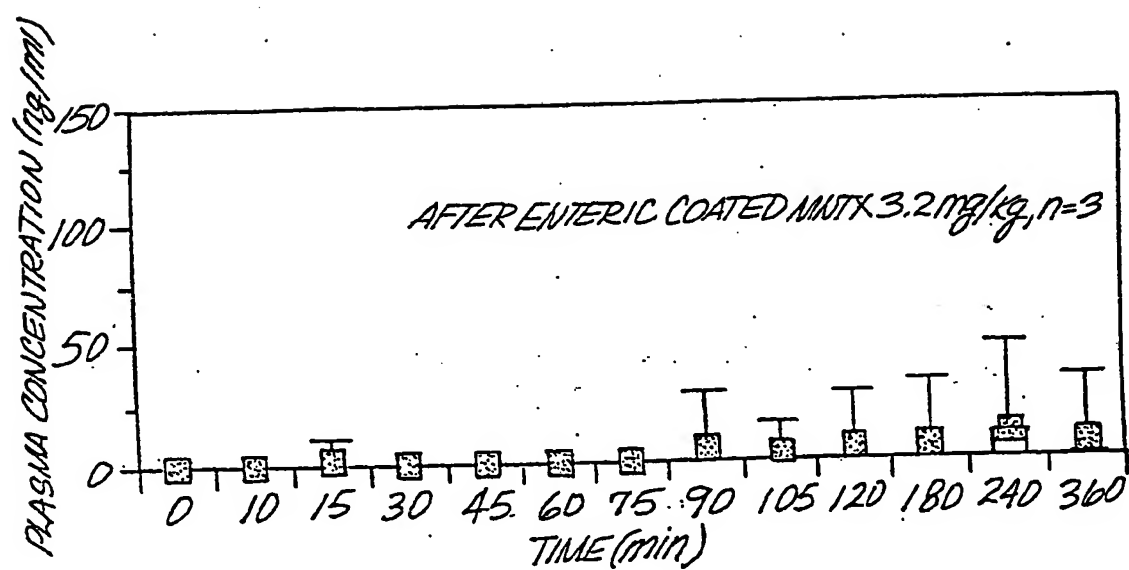
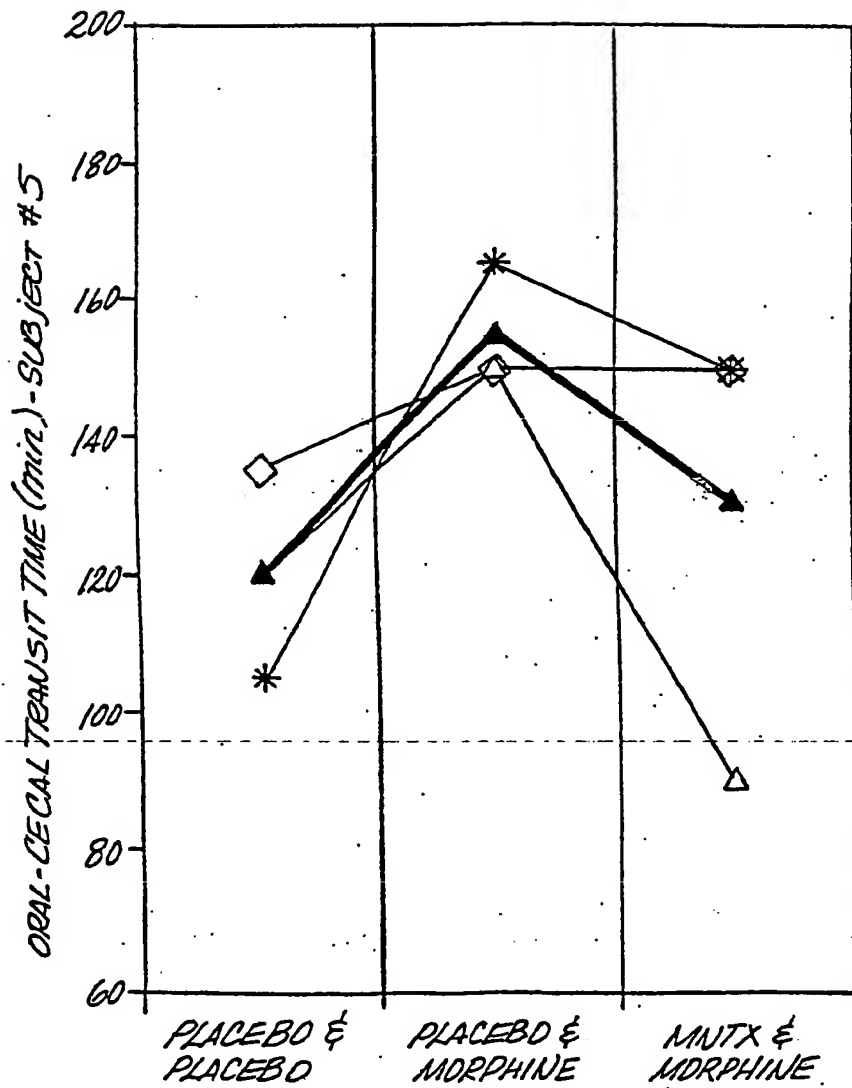


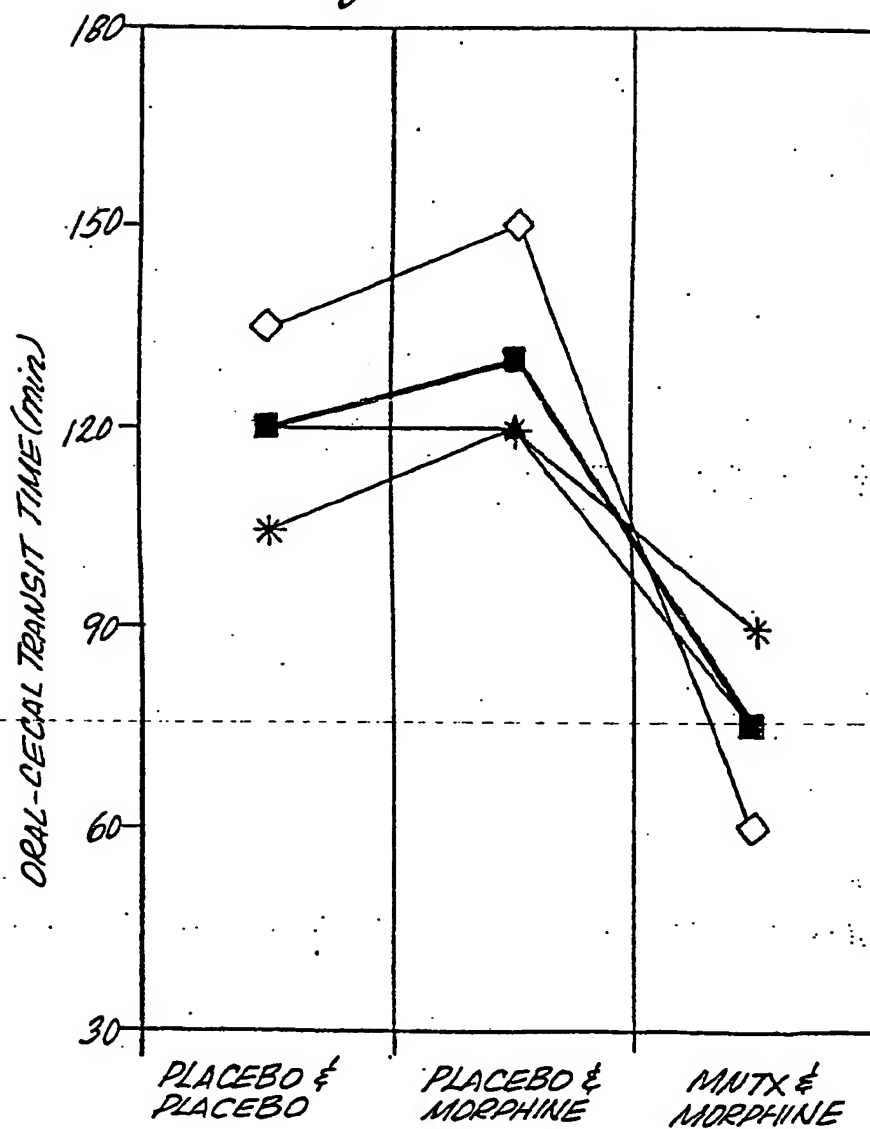
Fig. 1C

Fig. 2



$n=3$   
MORPHINE = IV MORPHINE 0.05 mg/kg  
MNTX = REGULAR MNTX 6.4 mg/kg

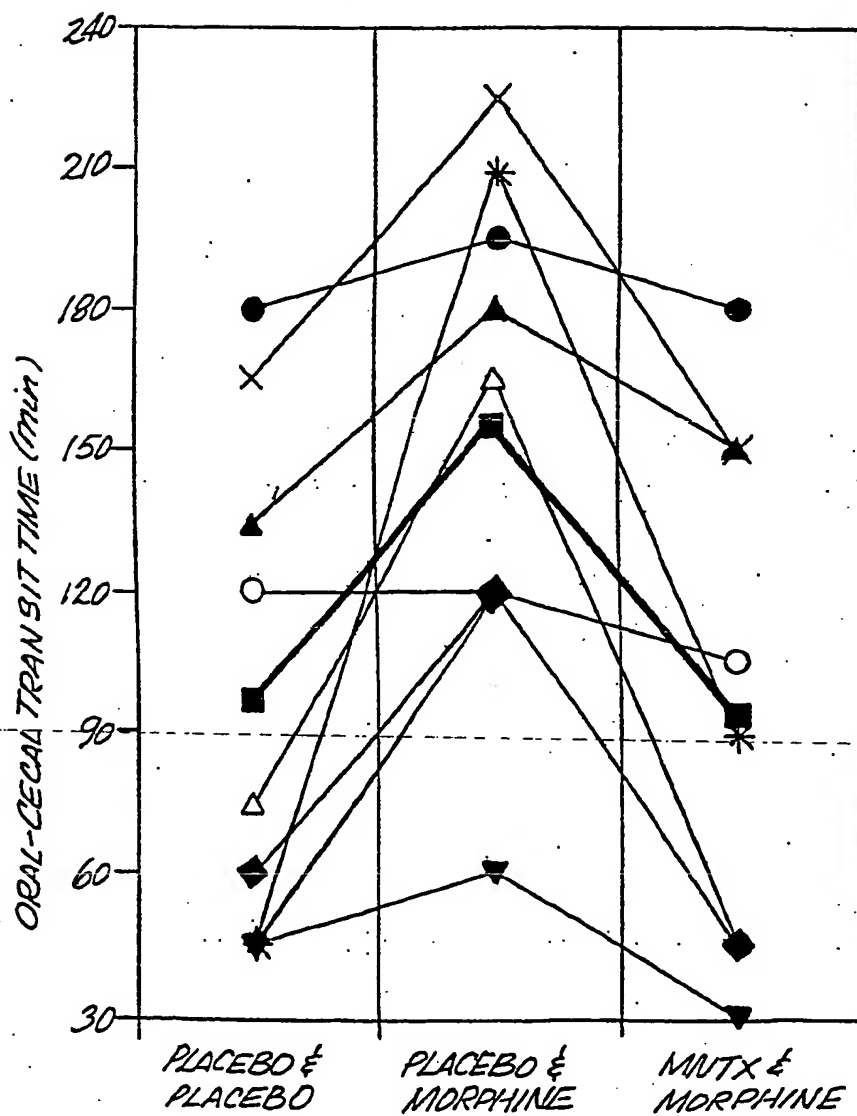
Fig. 3



$n=3$   
MS = IV MORPHINE 0.05 mg/kg  
MNTX = ENTERIC COATED MNTX 6.4 mg/kg

5/5

Fig. 4



$n=9$   
MORPHINE=IV MORPHINE 0.05 mg/kg  
MNTX=ENTERIC COATED MNTX 3.2 mg/kg

## THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for preventing or treating opioid-induced side effects comprising administering an enterically coated quaternary derivative of noroxymorphone to a patient prior to, subsequent to or simultaneously with the administration of an opioid.
2. The method of claim 1, wherein the enterically coated quaternary derivative of noroxymorphone is administered to a patient simultaneously with the administration of an opioid.
3. The method of claim 1 or 2, wherein the quaternary derivative of noroxymorphone is methylnaltrexone.
4. The method as recited in claims 1, 2 or 3 wherein the opioid-induced side effect is one or more selected from the group consisting of dysphoria, pruritus, urinary retention, and gastrointestinal dysfunction.
5. The method of claim 4, wherein the gastrointestinal dysfunction is gastrointestinal emptying, inhibition of gastrointestinal motility and/or constipation.
6. The method as recited in claim 3, wherein the methylnaltrexone is administered at a dosage of about 0.1 to about 40 mg/kg of body weight.
7. A method of treating or preventing opioid-induced side effects comprising administering a quaternary derivative of noroxymorphone to a patient, wherein the patient's peak plasma levels of the quaternary derivative of noroxymorphone do not exceed about 50 ng/ml.
8. The method of claim 7, wherein the patient's peak plasma levels of the quaternary derivative of noroxymorphone do not exceed about 25 ng/ml.
9. The method of claims 7 and 8, wherein the opioid-induced side effects are selected from the group consisting of: dysphoria, reduced urinary retention, and gastrointestinal dysfunction.

10. The method of claim 9, wherein the gastrointestinal dysfunction is gastrointestinal emptying, inhibition of gastrointestinal motility and/or constipation.
- 5 11. The method of claims 8, 9, and 10, wherein the quaternary derivative of noroxymorphone is methylnaltrexone.
12. A pharmaceutical composition used for preventing or treating opioid-induced side effects comprising an enterically coated quaternary derivative of  
10 noroxymorphone and a pharmaceutically-acceptable binder.
13. The pharmaceutical composition of claim 12 wherein the enterically coated quaternary derivative is in the form of a pill, tablet, capsule, or granule.
- 15 14. The pharmaceutical composition of claim 12 wherein the enteric coating dissolves substantially immediately upon contact with the digestive juice of the intestine.
15. The pharmaceutical composition of claim 12 wherein the enteric coating is a  
20 time release coating.
16. The composition of claims 12-15, wherein the quaternary derivative of noroxymorphone is methylnaltrexone.
- 
- 25 17. The pharmaceutical composition of claim 16, wherein the enteric coating is selected from the group consisting of hydroxyalkyl celluloses and their aliphatic esters, carboxyalkyl celluloses and their salts, polycarboxymethylene and its salts and derivatives, polyvinyl alcohol and its esters, polycarboxymethylene copolymer with sodium formaldehyde carboxylates, poly-vinylpyrrolidone,  
30 methacrylic acid copolymer, methacrylic acid copolymer type C, polyvinyl acetate phthalate, and polyethylene glycol and its esters.
18. The pharmaceutical composition of claim 17, wherein methylnaltrexone is coated with methacrylic acid copolymer enteric coating.
- 35



19. The pharmaceutical composition of claim 18, wherein methylnaltrexone is administered at a dosage of about 0.1 to about 80 mg/kg of body weight.
20. Use of a quaternary derivative of noroxymorphone for the manufacture of a medicament for treating or preventing opioid induced dysphoria, opioid induced pruritus or opioid induced urinary retention.
21. A use as claimed in claim 20, wherein the medicament is for administration to a patient;
- a) prior to the administration of an opioid and the method is for preventing opioid induced dysphoria, opioid induced pruritus or opioid induced urinary retention; or
- b) subsequent to administration of an opioid and the method is for treating opioid induced dysphoria, opioid induced pruritus or opioid induced urinary retention.
- c) simultaneously with the administration of an opioid and the method is for preventing or treating opioid induced dysphoria, opioid induced pruritus or opioid induced urinary retention.
22. Use of a quaternary derivative of noroxymorphone for the manufacture of a medicament for preventing or treating non-opioid induced gastrointestinal dysfunction, administration of the medicament to a patient being prior to, simultaneous with or after the onset of gastrointestinal dysfunction.
23. The method of claim 22, wherein the gastrointestinal dysfunction is gastrointestinal emptying, inhibition of gastrointestinal motility and/or constipation.
24. Use of a quaternary derivative of noroxymorphone for the manufacture of a medicament for treating or preventing non-opioid induced inhibition of gastric emptying, non-opioid induced inhibition of gastrointestinal motility or non-opioid induced constipation.
25. A use as claimed in claim 24, wherein the medicament is for treating or preventing idiopathic constipation.

26. A use as claimed in claim 24, wherein the medicament is for treating inhibition of gastrointestinal motility induced by an endogenous opioid.
- 5 27. A use as claimed in any of the claims 20-26, wherein the medicament is administrable by a parenteral route.
28. A use as claimed in any of the claims 20-26, wherein the medicament is administrable by a route selected from the group consisting of intravenous,  
10 intramuscular, transmucosal, transdermal, and oral administration.
29. A use as claimed in any of the of the claims 20-26, wherein the quaternary derivative of noroxymorphone is coated with an enteric coating.
- 15 30. A use as claimed in claim 29, wherein the quaternary derivative of noroxymorphone is formulated as a tablet and the tablet is coated with an enteric coating.
31. A use as claimed in any of the claims 20-26, wherein the quaternary derivative  
20 of noroxymorphone is methylnaltrexone.
32. A use as claimed in claim 31, wherein the medicament is formulated to provide  
----- methylnaltrexone in-tablet-form at a dosage of 0.1 to 40.0 mg/kg body weight. -----
- 25 33. A use as claimed in claim 28, wherein the medicament is formulated to provide a methylnaltrexone dosage of 0.03 to 1.0 mg/kg body weight by transmucosal, intravenous or intramuscular administration, 1.0 to 10.0 mg/kg by transdermal administration or 0.1 to 80 mg/kg body weight by oral administration.

Dated this twentieth day of June 2003

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F B RICE & CO

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